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Investigating the structure–diffusion–bioactivity relationship of strontium containing bioactive glasses using molecular dynamics based computer simulations

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ABSTRACT

Molecular dynamics simulations have been used to study the effect of SrO/CaO substitution and composition on the glass structure and ionic diffusion behaviors of bioactive glasses. The glass compositions studied include three bioactive glass compositions with silica content ranging from 46 to 65 mol% that covers a wide range of bioactivity. The local environments around modifier cations such as strontium, calcium and sodium and the network structures such as Q_n distribution and network connectivity of these glasses were determined as a function of composition. Ionic diffusion was studied by calculating the mean square displacement (MSD) to obtain self-diffusion coefficients and studying diffusion at different temperatures to obtain diffusion energy barriers. The ionic diffusion properties, together with the glass structure features, were used to understand the difference in dissolution and bioactivities of these glasses. It was found that sodium ions had a much higher diffusion coefficient and lower diffusion energy barrier than calcium and strontium ions and the diffusion coefficient of modifier cations decreases by several orders of magnitude with increasing silica content and decreasing bioactivity. The preexponential factor was found to dominate the values of cation diffusion coefficients while diffusion energy barriers are relatively insensitive to composition change in the glasses studied.

1. Introduction

Bioactive glasses as a relatively new type of materials for biomedical applications have attracted considerable attention in both glass science and biomedicine community [1,2]. These inorganic glasses, with components not too different from our window and container glasses, when formulated in a carefully selected composition range as first discovered by L. Hench [1], show intriguing bioactivity that allows them to form intimate bonding to soft and/or hard tissues and their dissolution ionic products capable of triggering gene expression and osteogenic properties [1,2]. As a result, these glasses find applications in bone repair, tissue engineering, toothpaste additives, bioactive coatings for bioinert load bearing metal/alloy implants, and other biomedical applications [1–3].

Fundamental understanding of the structure–property (especially bioactivity) relationship of these novel glass materials relies on detailed information of the atomic structures and their correlation to other properties [4,5]. It is also critical to achieve the so called rational design of glass compositions for emerging biomedical applications. Atomistic computer simulations play an increasingly important role in understanding the structure, dissolution and bioactivity of glasses for biomedical applications [4–6]. This is partly due to the amorphous nature of bioactive glasses that makes atomistic simulations one of the best methods to study their structures and properties. This is also related to the fact that the time and length scales that are critical to structural and dynamical features that govern dissolution and bioactivity are well in the range that are accessible to the methods such as molecular dynamics simulations [6], especially the rapid increase of computing power and development of algorithms/methodologies. Simulations have now greatly contributed to understanding of bioactive glasses, which can be reflected in a large increase in the number of publications of bioactive glass simulations in recent years [4–6,20–22].

Nevertheless, there are also several notable challenges in the simulations of bioactive glasses, or glass materials in general, using atomistic simulation methods. Molecular dynamics (MD) simulations are a method that is widely used to generate glass structure models. The time accessible in MD is determined by two factors: the number of steps that are governed by the accessible computing resources and the time step of MD simulations which is determined by the accuracy of integration of Newton's equation of motion. The former for a system of a couple of thousand atoms can be a few millions of steps while the later, depending on the potentials used, ranges from a fraction to a few femto-seconds, which leads to accessible time in the nano-second range in a normal MD simulation. The accessible time in term determines the cooling speed during glass formation that is several orders

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higher than experiments. It was found that some structure features are more sensitive to cooling rate than others [5,7]. For example, Du and Xiang found that the cooling rate in MD simulations had an impact on the fraction of orthophosphate groups in 45S5 bioactive glasses [5], which was supported by a later MD studies [7]. Another challenge is during the study of dynamic properties using MD simulations. Like bio-mineralization and related biological processes, dissolution of bioactive glasses happens at an ambient temperature range in a biological fluid environment. It is well accepted that the initial stage of dissolution is ionic diffusion and ion exchange of ions in the glass with proton or hydronium in the solution. To study the diffusion in glasses at an ambient temperature is difficult as the structure is rigid and diffusion as a thermally activated process happens as rare events. MD simulations can provide mechanistic understanding of diffusion in glasses [8,9], however studying diffusion at room temperature poses significant challenges as a result of this rare event behavior as it takes a large number of steps for one event to happen. Methods such as umbrella sampling or accelerated MD methods have been developed but require specialized programs and usually limited to relatively simple systems. A commonly used way to overcome this challenge is to use a higher temperature in simulations to speed up the diffusion but the temperatures were carefully maintained below glass transition temperatures so the glass structure remains rigid [5,7]. It is thus required to carefully interpret the obtained results.

Recent experimental studies have shown that the introduction of certain types of trace elements to bioactive glass compositions can lead to enhanced bio-functionality: antibacterial (Ag), osteogenesis (blood vessel growth) (Cu), and osteogenesis (Sr), for scaffolds in tissue engineering [3]. Strontium in particular was found to facilitate bone tissue growth due to the effect of strontium ions release from the glass which uniquely enhance osteoblast cell proliferation and inhibit bone absorption osteoclast cell proliferation [10–13]. Strontium containing bioactive glasses, especially when introduced through SrO/CaO substitution, have similar glass structure and dissolution behaviors as compared to the original composition due to chemical similarity of Sr^{2+} and Ca^{2+} but provide bone growth enhancement due to the beneficial effect of Sr^{2+} ions. MD simulations have also been used to understand the strontium local environment and diffusion behaviors in SrO containing bioactive glasses [4,5,13].

The purpose of this paper is to use classical molecular dynamics simulations to study the structure and diffusion behaviors of three bioactive glass compositions to represent a wide range of bioactivity. The 45S5 composition has the lowest silica content (46 mol%) and is the most bioactive. It can be dissolved in the body fluid environment and bonds to both soft and hard tissues. The 55S4.3 composition containing 55 mol% silica can bond hard tissue but not soft tissue, while 60S3.8 contains 60% silica and is bioinert and can bond to neither soft nor hard tissue. In addition to the base bioglass compositions, 5 mol% SrO/CaO substitution was introduced in these glasses to understand the Sr local environment and diffusion as a function of composition. The short and medium range structure features such as Q_n distribution, the network connectivity, and cation local environments will be studied. Modifier cation ionic diffusion will be studied using mean square displacement calculations for temperatures below the glass transition temperature.

2. Simulation details

Three base bioglass compositions: 45S5, 55S4.3 and 65S3.8 and those with 5 mol% SrO/CaO substitutions were studied using classical molecular dynamics simulations. In the original notation “45” “55” and “65” meant the weight percentage of SiO_2. The base glass compositions of each glass sample are listed in Table 1. And the 45S-5Sr, 55S-5Sr and 65S-5Sr represent corresponding 45S5, 55S4.3, 65S3.8 compositions with 5 mol% of CaO substituted by SrO. This level of substitution was commonly used in experimental studies, which found that an appropriate amount of strontium can increase bone mass and strength while decreases the chance of fracture while to a high level of Sr will result in bone composition and property change, especially when intake of Ca is limited [14].

The simulations were performed on systems of around 3000 atoms in cubic simulation cells with the initial density from the experimental values [1]. Initial coordinates of all the atoms were randomly generated inside a cubic simulation box with periodic boundary condition. The interactions between atoms were based on the Born model of solids with a set of effective partial charge pair-wise potentials [15–17]. The partial charge potentials take into consideration of partial covalency of silicate network and have been successfully applied to silicate, aluminate, phosphate and several mixed former glass systems. These potentials have also been used to simulate SrO/CaO substituted 45S5 bioactive glasses and showed good agreement with experimental diffraction data and properly reproduced the trend of density change as a function of the level of SrO/CaO substitution [4,5]. Details of the potentials including partial atomic changes and Buckingham short range interaction parameters can be found in ref. [4,5]. Long range Coulombic interactions between the charged particles were calculated using the Ewald summation method with a cutoff of 10 Å and precision of 10^{-6} eV. Short range interactions in the Buckingham form were modified to include corrections at short interatomic distances. The Verlet algorithm with a time step of 1 fs was used to integrate the equations of motion. The generation of glass structure was performed by the simulated melt and quench process with a combination of the isothermal isobaric ensemble (NPT) and then microcanonical ensemble (NVE). The initial random structure was first relaxed at 0 K and then heated to 4000 K to guarantee adequate mixing. A 200 ps NPT run with subsequent 200 ps NVE equilibration were performed at each temperature. After equilibration at 4000 K, the melt was gradually cooled to 300 K through 3500, 3000, 2500, 2000, 1660, 1429 and 1000 K with a nominal cooling rate of 0.5 K/ps. For intermediate steps the trajectories under the NVE run were recorded every 20 steps for the calculations of diffusion coefficient. At 300 K, configurations of every 50 steps in NVE ensemble for a period of nearly 400 ps were recorded for further structural analysis.

3. Results

3.1. Structure of bioactive glasses

3.1.1. Q^n distribution and network connectivity

Representative structure of simulated bioactive glasses is shown in Fig. 1 with a snapshot of the glass 55S-5Sr. Glass network forming

Table 1
Composition of simulated bioactive glass samples, density of final glass, and simulation cell information.

Glasses	SiO_2	Na_2O	CaO	SrO	P_2O_5	Density	O	Si	P	Na	Ca	Sr	Cell size
	(Mol%)					(g/cm^3)	(Number)						(Cubic, Å)
45S5	46.1	24.4	26.9	0.0	2.6	2.66	1565	461	52	488	269	0	33.75
45S-5Sr	46.1	24.4	21.9	5.0	2.6	2.74	1565	461	52	488	219	50	33.84
55S4.3	56.5	19.4	21.5	0.0	2.6	2.55	1655	551	52	402	222	0	34.25
55S-5Sr	56.5	19.4	16.5	5.0	2.6	2.64	1655	551	52	402	172	50	34.30
65S3.8	66.9	14.5	16.0	0.0	2.6	2.48	1773	669	52	290	160	0	34.58
65S-5Sr	66.9	14.5	11.0	5.0	2.6	2.50	1773	669	52	290	110	50	34.95

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